majority of the immunoglobulin G. Support for this amendment is found in the application at page 4, lines 19-22.

Claim 17 has been amended to refer to a system instead of a kit.

I. Prior art Rejections

Claims 1-23 were rejected under 35 U.S.C. 103 as obvious over U.S. Patent No. 4,708,713 to Lentz, U.S. Patent No. 5,523,096 to Okarma, et al., and U.S. Patent No. 5,861,483 to Wolpe. These rejections are traversed.

The Invention

There are multiple inventions described in this application. The first is that the prior art ultrafiltration process, the subject of U.S. Patent No. 4,708,713, or a filter having a lower molecular weight cutoff, as discussed above, can be used in combination with other agents, where the ultrafiltration induces remission, and the other agents maintain the patient in remission (claims 9-23, limited to the lower molecular weight filter). The second invention, which is the invention claimed in this pending application, and the specific device defined by claims 1-9, is the discovery that one can use a filter to selectively remove molecules of less than 120,000 daltons from the blood of a patient, not including immunoglobulin G, and induce remission in a cancer or other type of chronic disease. The filtration process removes material which is apparently produced by the cancer to prevent the patient from killing the tumors.

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The examples demonstrate that the adjunctive method was effective in treating cancer patients. The first example at pages 12-13, was a lung cancer patient who had failed conventional chemotherapy. Filtration alone reduced the tumor size and number. The second example at page 13 described a woman with metastatic breast cancer who had failed radiation and conventional chemotherapy. Filtration was used to enhance immune attack on the tumors (leading to inflammation, see page 13, lines 12-16), then thalidomide, an anti-angiogenic compound, used to further resolve the tumors. Example three at pages 13-14 was a patient with metastatic melanoma who was treated initially with filtration to induce tumor inflammation, then treated with thalidomide to induce remission. Example 4 at page 14 is a patient with metastatic adenocarcinoma who had failed treatment with taxol, ciplatin and etoposide. The filtration was used to cause tumor inflammation, then followed with thalidomide to cause further tumor regression.

The Filter Size of the Lentz Patent and the Present Application are Different

One of the questions raised at the Board of Appeals hearing (which had not previously been raised by the examiner) was exactly what filter was used in the examples. Dr. Lenz stated that the filters were filtration devices similar to those used for kidney dialysis, but modified as to the pore size to have a cutoff of approximately 120,000 daltons, so that the immunoglobulins (IgM, IgG) would be retained and given back to the patient, both so that they would not have to be replaced which is expensive but also because the patient's own immunoglobulin was believed to enhance the immune

reaction against the tumor cells. A Declaration under 37 C.F.R. 1.132 by Dr. Lentz which provides the details of these filtration devices as discussed at the Board hearing is being submitted under separate cover.

One of the other issues raised at the Board of Appeals hearing was how the prior art filter described in U.S. Patent No. 4,708,713 to Lentz could have such similar parameters to the parameters of the claimed filters, yet have different molecular weight cutoffs. The Board states beginning on page 6, "a suitable filter having a molecular weight cutoff of 120,000 daltons or less will have a pore size of 0.03 microns and a thickness of less than 25 microns and preferably less than 10 microns." (referring to page 4, lines 19-23). However, the application also states that the sieving coefficient should be between 10 and 30%, for this pore size to have the desired cutoff. The application further states that if the filter is a capillary membrane filter it should have a pore size between 0.02 and 0.05 microns, and that it should have a pore size of between 0.04 and 0.08 microns if it is a parallel plate filter (page 4, lines 12-16). More relevantly, the patent application states "The actual pore size that yields the desired cutoff of approximately 120,000 daltons is determined based on the fluid flow geometry, shear forces, flow rates, and surface area" (page 4, lines 16-19).

In contrast, the Lentz patent says at col. 4, lines 2-6, "The blood fraction having low molecular weight components, e.g. those having molecular weight less than about 1,000,000 Daltons, preferably less than about 200,000 Daltons, passes through the

membrane..." and at col. 4, lines 56-68, "The ultrafilter medium or membrane should have an effective pore size less than about 15 microns in diameter in order to selectively separate the desired low molecular weight components from the blood. A filter media having an effective pore size of about 0.03-0.07 microns will separate components with molecular weight less than about 200,000 Daltons. A membrane with an effective pore size less than about 0.03 micron is needed to separate blood components with molecular weights less than about 30,000 Daltons." Further, the patent states at col. 5, the various other factors to adjust: flow rate, differential pressure and membrane thickness.

Accordingly, looking solely at pore size, the Lentz patent states the following:

Lentz Patent		Lentz patent application	
pore size	molecular weight cutoff	pore size	molecular weight cutoff
0.07-0.1 microns	1,000,000		
0.03-0.07 microns	200,000		
		0.03 microns	120,000
		0.02 and 0.05 microns	120,000
		0.04 and 0.08 microns	120,000
< 0.03 microns	30,000		

There is nothing inconsistent between the patent and the patent application, as this comparison shows. As Dr. Lentz stated at the hearing, and which is further supported by the materials submitted with this reponse ("Filtration Fundamentals: Is Knowledge of

Filter Technology Something You Let Fall Through the Cracks?" by Bob Sinclair, The Scientist 12(19):18 (September 1998); "Laboratory Filtration Concepts" by Pall Live Sciences), it is well known that *pore size is only one factor determining molecular weight cutoff of a filter.* One cannot compare only the pore sizes of two different filters to determine the molecular weight cutoff. The materials the filters are made of, the thickness of the filter, the shear rates, the surface configurations, the materials to be separated, the flow rates, and many other variables determine the actual molecular weight cutoff. Therefore one *cannot* say that because the Lentz patent recites a range of pore sizes and the present application recites a similar range of pore sizes, that they will have the same molecular weight cutoffs.

NOT claimed

The only way to actually compare cutoffs is to read the Lentz patent and compare what it teaches with the teachings of the present application. Lentz discloses using a filter to remove all blood components of 200,000 mw or less to treat cancer patients (see col. 6, lines 34-46. While favorable results were obtained, the patient loses all of the IgM, G and IgA antibodies which have a molecular weight greater than 120,000, but less than 200,000 daltons (as shown by the attached excerpt from "General Immunology" by Herman N. Eisen, page 78), which are extremely important to fight infection. Since infection is a major problem for cancer patients, this method would not have been developed if the patentee had believed that one did not have to remove the immunoglobulins. However, it simply had not been determined even as of the issue date

of the '713 patent (1987), what component(s) was being removed by the procedure, which allowed the patient to then fight off the cancer.

As Dr. Lentz further explained at the Board hearing, it has taken years of subsequent work to determine that the "bad" component which is removed by the procedure is a relatively low molecular weight component, allowing the substitution of a filter with a lower molecular weight cutoff. The Lenz patent speculates at col. 6, lines 39-46, that it is a component of a similar weight to an immunoglobulin which protected the tumor; col. 4, lines 65-68, lead one to believe that it is a component of less than 30,000 which is the tumor protective agent. In fact, as Dr. Lentz has subsequently learned, it is neither, but the soluble tumor necrosis receptor fragments secreted by the tumor that protects the tumor. The size of these fragments are approximately 55,000 and 75,000 daltons (see, U.S. Patent No. 6,231,536; and Ammirato, et al., Front. Biosci. 1:6:B17-24(2001)). See also Selinsky, et al., Immunology 94:88-91 (1998).

In summary, the evidence strongly supports the conclusion that the filter of the Lentz patent is ***not*** inherently the same as the claimed filter. The Lentz patent explicitly teaches that the filter must remove a complex that is approximately 120,000 daltons. The claimed application explicitly requires that the filter ***not*** remove molecules having molecular weights of approximately 120,000 daltons. The pore sizes, as well as the other features of the filters described in the Lentz patent and the present application, are ***not*** overlapping, but indicate that there are ranges of pore sizes that will result in different

molecular weight cutoffs, depending on the filter construction. The evidence now before the examiner and the Board supports the statements that have been made in the application and during prosecution in this regard.

There is no Motivation to Combine Ultrafiltration with other Treatments

There is no disclosure of combining filtration with other methods to induce further remission or maintain remission. The patients that are described in the examples had *previously been treated with every other type of treatment, and had failed those treatments. They had been treated with chemotherapy and with radiation and their cancers continuted to grow and destroy their bodies.* Nothing has been cited that would lead one skilled in the art to say "yes, these treatments all failed before, but now that ultrafiltration has caused the tumors to shrink in size, now we should use these other treatments again, and they will be expected to work." This is absurd. One skilled in the art would say that once a patient has "failed" a therapy – i.e., their cancer has failed to respond to the treatment, there is absolutely no motivation to think the cancer might suddenly become susceptible to the treatment.

See, for example page 12, lines 25-29, "These tumors had also failed methotrexate, adriamycin, ifosphomide, and dactinomycin." See, for example, page 13, lines 6-9, "Mrs. J.R. is a 44 year old lady who had metastatic breast cancer that had failed radiation therapy and treatment with chemotherapeutic agents: cytoxan, adriamyxin, 5-

FU, taxol, cis-platin, navalbine, tamoxifin and arimedex." See, further page 14, lines 8-11, "His tumors had failed to respond to taxol, cis-platin and etoposide."

This evidence totally teaches away from any such treatment. Yet these exact same patients, all of whom responded to the ultrapheresis, showed further tumor reduction following adjunct treatment. For example, page 14, lines 15-18, "There was a 50% reduction in the primary tumor in the lung and liver. Thalidomide was then started at 200 mg each night. One month later, the scans revealed further reduction in the tumors in the lung and liver. The patient's pains have all been resolved and he is asymptomatic at this time."

Note, these examples demonstrate that ultrapheresis was effective even when the patient had failed chemotherapy, including with antiangiogenic compounds, as well as radiation. Moreover, the examples demonstrate that even further benefit could be achieved by then treating the patients with chemotherapeutic agents even though they had previously failed treatment with chemotherapeutic agents. Nothing in any of the cited art could possibly lead one skilled in the art to such an outcome.

Moreover, in response to the Board's statement that applicant does not show an effect greater than what is considered to be the closest prior art, this is clearly wrong.

The examples all start with treatment using ultrapheresis. Regardless of whether or not there is a difference in tumor reduction due to the molecular weight cutoff (impossible to tell, since each patient responds differently and it would be unethical to

treat a human patient first with one filter, and then the second having a lower molecular weight cutoff), the principle difference based on the molecular weights is that one has to treat patients in the first case with whole plasma to restore their immunoglobulins (the issue regarding non-obviousness is that one could not predict treatment with the lower molecular weight cutoff would be efficacious; not whether or not it produced better or different results). This supplementation is extremely expensive. What is significant, and extremely unexpected, is that further tumor reductions were then observed when the patient was treated with a chemotherapeutic agent. As discussed above, these patients had all failed treatments with chemotherapeutic agents. There was absolutely no reason to believe they would be responsive, in fact conventional wisdom would lead one skilled in the art to believe they would *not* be responsive.

Chen teaches that soluble TNF-alpha receptors suppress the patients ability to fight cancers. Soluble TNF-alpha receptors are 55,000 and 75,000 daltons in size (page 541, col. 1). Contrary to the Board's opinion, Chen does not teach that one could remove the soluble TNF-alpha receptors and that would reduce the tumors.

If it were so obvious that one could just remove the soluble TNRFs, then one can be certain that Chen would have suggested. Instead, Chen is making an observation that would lead one skilled in the art to believe that sTNFRs must be part of a much more complex situation. *Chen is not a study in humans or even tumors, but a study of cell-cell interaction in cell culture.* It is well known that cell culture is not predictive of what

might occur in a patient, but in this case, the sTNFRs are not even removed from the cell culture, they are merely measured and found to be released by the cells. It is speculated that the factors may play a role "These data suggest that soluble TNF receptors may play a role in the mechanism by which malignant gliomas downregulate the effects of infiltrating immune-competent cells."

This is NOT a teaching that tumors release these factors; that these factors play a physiological role; nor that altering their levels would have any significance in a patient.

The Board decision totally ignores its own standards in reaching such a conclusion. It leaps from a study that says tumor cells in culture produce soluble TNFRs that *"may play a role in the mechanism by which malignant gliomas downregulate the effects of infiltrating immune-competent cells."* to the conclusion that removal of sTNFs using ultrafiltration will cause tumor reduction in patients, even when the tumors have metastasized throughout the body and failed all accepted chemotherapy and radiation therapy. Such a conclusion defies common sense, much less the law.

Therefore the combination of Lentz with Chen is **not** the same as what applicant is claiming. Moreover, there is nothing that would lead one to believe that only the smaller molecular weight molecules could be removed and the cancer be treated effectively, based on Lentz. Accordingly, one skilled in the art would be led **away** from the combination of Lentz and Chen, **not** to a **modified combination.**

Okarma, et al., describes removal of cytokines and other factors using silica to absorb the materials. The reason applicant treated patients with ultrafiltration was because he did not know what, or how many, factors had to be removed to treat tumors, but made cutoffs in an effort to keep certain components based on their molecular weight. Okarma, et al. does something different: He removes factors of all molecular weights based on binding to silica-based absorbents.

There is nothing that would lead one to combine Okarma, et al., with Lentz, modify Lentz to remove lower molecular weight blood components (i.e., molecular weights 120,000 daltons or less rather than 200,000 daltons), modify Okarma et al., to leave in the cytokines (and everything else bound by silica but which is less than 120,000 daltons) but remove the cytokine inhibitors removed by ultrafiltration, and have any expectation of success.

Wolpe states that certain factors are known which enhance the immune system. Wolpe does not address the issue of whether or not there is an immunosuppressive component having a molecular weight in the critical range between that which is now

claimed and that which is taught in the thirteen year old patent to Lentz, prior to many subsequent studies which were required to determine that the immunosuppressive element does **not have a molecular weight similar to that of an immunoglobulin or immunoglobulin complex.** The difference is important: by using the lower molecular weight cutoff, the patient can keep their own immunoglobulin, helping them to more successfully fight off infection.

II. Rejections under 35 U.S.C. 112

Claims 10-15, 17 and 23 were rejected under 35 U.S.C. 112 on the basis that the specification is allegedly non-enabling. These rejections are respectfully traversed.

Rejection of Claim 17

Claim 17 was rejected on the basis that the Board did not understand how a kit could include radiation. The claim has therefore been amended to refer to a system which includes both a filtration devices and means for radiation. ? is not claimed.

Rejection of Claim 21

Claim 21 was rejected as being an absorbent column with a molecular weight cutoff. This rejection is traversed in view of the accompanying materials which show that it is routine to make filtration devices having molecular weight cutoffs which can also have ligands (such as antibodies) bound to the filtration material that will selectively remove the receptors. This kind of a device is routine in the art and been used commercially for decades, although not in the claimed context.

This embodiment is described in the application at page 11, beginning at line 20, to page 12, line 2. As demonstrated by the enclosed paper by Selinsky, et al., those skilled in the art have had no trouble in making such a device.

The Board's statements with regard to the number of patients treated, and lack of published evidence, on page 16, is totally inappropriate and unsupported in the law. There is no legal requirement to say how many patients have been treated. Indeed, there is no legal requirement for any patients to have been treated. This is not an FDA approved treatment. Each one of these patients was treated following review by an independent hospital review board which grants a compassionate use of the procedure solely after review of the individual patient's records. Applicant has not yet obtained the financial resources to conduct large scale clinical trials which will cost millions of dollars to obtain approval.

The court stated in *In re Brana*, "Usefulness in patent law and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." *In re Brana*, 51 F.3d 1560, 1568 (Fed.Cir. 1995). The law is explicitly clear, however, as to what pharmaceutical utility does **not** require. Pharmaceutical utility does not require human testing[1] or animal testing.[2]

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[1] *In re Jolles*, 628 F.2d 1322 (CCPA, 1980); *In re Krimmel*, 292 F.2d 948 CCPA, 1961); *Cross v. Iizuka*, 753 F.2d 1040 (1985); and *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995)

[2] *In re Krimmel*, 292 F.2d 948 CCPA, 1961) and *Cross v. Iizuka*, 753 F.2d 1040 (1985)

Pharmaceutical utility does not require a showing of therapeutic safety,[3] and it most certainly does not require a showing of efficacy.[4] The reasons for this are policy based because it is in the best interest of the public, the benefactors of the inventive material, to have the choice of when, how, and why to use the disclosed material[5]..

[3] *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995) and *In re Irons*, 340 F.2d 974, 978 (CCPA 1965)

[4] See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); Ex parte *Jovanovics, 211 USPQ* 907 (Bd. Pat. App. & Inter. 1981)

[5] *In re Brana*, 51 F.3d 1560, 1568 (Fed.Cir. 1995) Not only does the public lose because of lost opportunity to utilize the invention, the public loses because of lost opportunity to benefit from further pharmaceutical research. Commenting on why the utility standard is what it is the *Brana* court stated, "Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many areas such as the treatment of cancer."

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RESPONSE UNDER 37 C.F.R. 1.196(b)

For the foregoing reasons, applicants submit that claims 1-23 are novel and nonobvious over the prior art. Allowance of claims 1-23 is earnestly solicited.

Respectfully submitted,

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